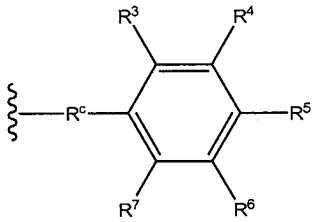
REMARKS/ARGUMENTS

I. Status of the Claims

Claims 1, 6, 8, 10-24, 26, 27, 30, 33, 34-39 are pending in this application. Claims 16-23 are withdrawn from consideration. Claim 38 is cancelled. Claims 1, 6, 8, 10-15, 24, 26, 27, 30, 33, 34-38 are currently under consideration. Claim 6 is amended to add the term "macrocyclic metal chelate is 1,4,7,10-tetraazacyclododecane-N,N',N",N"'-tetraacetic acid (DOTA)." This amendment adds no new matter and is fully supported throughout the specification, for example paragraphs 7, 239, and 240 of the specification. Claim 37 has been amended to add the term "sequence identity." This amendment clarifies elements of the sequence of the claimed antibody and adds no new matter.

Claims 40-42 are new and do not introduce new matter. Claims 40-41 list specific elements of the Markush group of claim 6 and add no new matter.

Claim 42 has been added to include the following structure:



Support for the structure can be found in paragraph 239 of the specification. In the claimed structure, element R^C has been substituted for element $(CH_2)_S$. R^C is defined as an unsubstituted unbranched alkyl linker. One skilled in the art would understand that the element $(CH_2)_S$ of the structure in paragraph 239, which includes a number of consecutive methylene (CH_2) groups, is interchangeable for the term unsubstituted unbranched alkyl linker.

Applicants respectfully request entry of the claims as amended.

II. Response to Claim Objections

Claim 39 is objected to under 37 CFR 1.75(c). Solely in the interest of furthering prosecution of this application and without conceding to the propriety of this objection, Applicants cancel claim 39, rendering this objection moot.

II. Response to Claim Rejections

Rejection under 35 U.S.C. 112, Second Paragraph

Claims 6, 8, and 33-36 are rejected under 35 U.S.C. 112, second paragraph as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Particularly, the Examiner states there is insufficient antecedent basis for the limitation "said substituted or unsubstituted DOTA."

For the sake of expedient examination, and without acquiescing to this ground for rejection, claim 6 has been amended to include the element "macrocyclic metal chelate is 1,4,7,10-tetraazacyclododecane-N,N',N",N"'-tetraacetic acid (DOTA)." In view of the amendment to the claim, Applicants request withdrawal of this rejection.

Rejection under 35 U.S.C. 112, First Paragraph

Claims 1 and 37 are rejected as allegedly lacking enablement under 35 U.S.C. 112, first paragraph. The Examiner states that the specification, ". . . does not provide enablement for an antibody comprising a first sequence having at least 95 % homology with SEQ ID NO: 1; a second sequence having at least 95% homology with SEQ ID NO: 5 . . . ." and that, ". . . the specification appears to be silent on any homologs of the amino acid sequences of SEQ ID NO: 1 and/or 5, wherein the variation occurs within the CDR's."

According to the Examiner:

> "In the instant case, it is well established in the art that the formation of an intact antigen-binding site of all antibodies requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs or hypervariable regions, which provide the majority of the contact residues for the binding of the antibody to its target epitope . . . . The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen specificity and affinity, which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites . . . . Even minor changes in the amino acid sequence of the heavy and light chain variable regions, particularly in the CDRs, may dramatically affect antigen-binding functions . . . .

The Examiner relies on Rudikoff et al. (*Proc. Natl. Acad. Sci* 1982; 79: 1979) as teaching that "the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function."

The Examiner concludes that "[i]t is unlikely that the antibodies as defined by the claims, which may contain less than the full complement of CDRs from the heavy and light chain variable regions of an antibody, have the required binding function," and that "[t]he specification provides no direction or guidance regarding how to produce antibodies as broadly defined by the claims. Undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone."

Applicants respectfully traverse this rejection. First, Applicants note that the standard for determining enablement is not based on the amount of guidance provided in the "written disclosure alone" (*i.e.*, Applicants' specification). Rather, there are several factors to consider when evaluating the enablement requirement and whether any necessary experimentation is "undue." These factors include: the breadth of the claims; the nature of the invention; the state of the prior art; the level of one of ordinary skill; the level of predictability in the art; the amount of direction provided by the inventor; the existence of working examples; and the quantity of experimentation needed to make or used the invention based on the content of the disclosure. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

The determination that "undue experimentation" is needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the above-noted factual considerations. *In re Wands*, 858 F.2d at 737. In the present case, upon weighing all of these factors, particularly the level of skill in the art and proven predictability of generating multiple antibodies that bind to the same target based on common CDR or variable region sequences, as discussed in detail below, claims 1 and 37 (drawn to an antibody having a first sequence having at least 95 % sequence identity with SEQ ID NO. 1 and a second sequence having at least 95 % sequence identity with SEQ ID NO. 5) are fully enabled.

A. Amino acid substitutions in the CDR are tolerated by antibodies

It is well known in the art that antibodies can tolerate amino acid substitutions in the CDR and still bind antigens. In fact, amino acid substitutions can actually *increase* the affinity of antibodies for antigens. Sharon (Structural correlates of high antibody affinity: Three engineered amino acid substitutions can increase the affinity of an anti-*p*-azophylarsonate antibody 200-fold, *Proc. Natl. Acad. Sci. USA*, **87**: 4814, (1990)) investigated the basis for the 200-fold difference in affinity between two hybridoma antibodies specific for the hapten *p*-azophylarsonate (Exhibit 1). The DNA sequence of the

lower-affinity antibody was converted into that of the higher-affinity one by oligonucleotide-directed mutagenesis. Eight amino acid substitutions were performed individually and in combination in the CDRs of the antibody. Sharon was then able to quantify the effect of substitutions on binding affinity. Sharon found that individual substitutions often *increased* antibody affinity.

In addition, Applicant has shown four amino acid substitutions in the CDR of the 2D12.5 antibody that are well-tolerated by the antibody, resulting in the irreversible binding of the antibody to a metal chelate with a reactive group of complementary reactivity to the reactive site on the antibody. See specification, page 62-65.

Contrary to Rudikoff (discussed in more detail below) these findings show that changes in amino acid sequence of the heavy and light chain variable regions, particularly in the CDRs, can be well-tolerated by antibodies in general. Moreover, as shown by Applicants, such changes demonstrably lead to operative antibodies within the scope of the presently claimed antibodies.

B. Amino acid substitutions within CDRs that do not affect antibody binding are fully enabled based on Applicants' specification and the knowledge in the art at the time of the invention

As amended, the presently pending claims encompass antibodies having a first sequence having at least 95 % sequence identity with SEQ ID NO. 1 and a second sequence having at least 95 % sequence identity with SEQ ID NO. 5. Applicants' specification fully enables one skilled in the art to produce antibodies with these characteristics.

The specification gives guidance as to the selection of sites to substitute: ". . . the mutation site and the nature of the mutation will be determined by the specific polypeptide of interest being modified and the structure of the reactive chelate to which the antibody binds. The sites for mutation can be modified individually or in series." See specification, page 34, lines 1-4, paragraph 128. The specification goes on to state that mutations can be made by (1) substituting first with conservative amino acid choices and then with more radical selections depending upon the results achieved; (2) deleting the target residue; or (3) inserting residues of the same or a different class adjacent to the located site, or a combination of option 1-3. Id.

The specification also describes methods for identification of certain residues or regions of the polypeptide of interest that are preferred locations for mutagenesis. See specification, page 33, lines 8-10, paragraph 129, addressing "Alanine-screening." In Alanine-screening, a residue or group of target residues are identified (*e.g.* charged residues such as arg, asp, his, lys, and glu) and replaced by a neutral

or negatively charged amino acid (most preferably alanine or polyalanine) to affect the interaction of the amino acids with the surrounding aqueous environment in or outside the cell. Those domains demonstrating functional sensitivity to the substitutions then are refined by introducing further or other variants at or for the sites of substitution. Thus, while the site for introducing an amino acid sequence variation is predetermined, the nature of the mutation per se need not be predetermined. For example, to optimize the performance of a mutation at a given site, alanine scanning or random mutagenesis is conducted at the target codon or region and the variants produced are screened for increased reactivity with a particular reactive chelate. Id.

The specification also gives guidance as to where substitutions can be made: "The sites of greatest interest for substitutional mutagenesis include one or two loops in antibodies. Other sites of interest are those in which particular residues of the polypeptide obtained from various species are identical among all animal species of the polypeptide of interest, this degree of conservation suggesting importance in achieving biological activity common to these molecules. These sites, especially those falling within a sequence of at least three other identically conserved sites, are substituted in a relatively conservative manner." See specification, page 36, lines 10-16. Applicants provide exemplars of conservative substitutions in Table 1 and give further guidance for making such substitutions throughout the sub-section headed, "Site-Directed Mutagenesis." See specification, page 34.

The specification also describes multiple methods of generating antibodies with amino acid substitutions using methods known in the art. See specification, page 34. For example, the specification explicitly sets forth art recognized methods of generating the claimed antibodies (*e.g.* site directed mutagensis, PCR mutagenesis, and cassette mutagenesis) and multiple reactive sites that can be introduced into the antibodies (*e.g.* cysteinyl residues, hystidyl residues, lysinyl and other amino terminal residues, arginyl residues, tyrosyl residues, aspartyl residues, glutamyl residues, glutaminyl residues, asparaginyl residues, proline residues, and lysine residues).

The specification also provides four working examples that describe generation of a 2D12.5 mutant, including identification of suitable locations for the amino acid substitution (*i.e.* reactive site) in the 2D12.5 antibody, mutagenesis of the 2D12.5 antibody to incorporate the reactive site, expression of the 2D12.5 antibody comprising the reactive site not present in the wild-type 2D12.5 and irreversible binding of the antibody to a metal chelate with a reactive group of complementary reactivity to the reactive site (mutation) on the antibody. See specification, page 62-65.

Moreover, routine techniques for testing whether such substitutions within the heavy and light chain variable regions affect or remove the binding activity of a given antibody were also well known and within the abilities of those of skill of the art at the time the present application was filed. See, *e.g.*, specification page 66, Example 3.

Accordingly, based on the knowledge and high level of skill of those in the art at the time of the present invention, and the relatively short sequences of the claims CDR and variable regions, it would not have been unpredictable, or have required undue experimentation, to have generated antibodies which retain binding having sequence modifications within the presently claimed variable or CDR regions.

C. The reference relied on by the Examiner does not establish unpredictability with respect to generating antibodies that bind to a metal chelate (DOTA) based on a common sequence as presently claimed

The Examiner relies on Rudikoff et al. in support of the position that "[e]ven minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding." Applicants respectfully disagree. Rudikoff et al. merely show that certain residues within antibody variable regions are critical for binding, not that it would have required undue experimentation or was beyond the abilities of one of ordinary skill in the art at the time of invention, to have identified such residues. Indeed, as discussed above, it was well within the abilities of one of ordinary skill in the art to have identified such residues, particularly within relatively short variable and CDR regions. Applicants respectfully note that the question of whether certain amino acid modifications can affect the binding affinity of an antibody is not the relevant inquiry in the present case. The relevant inquiry is whether sequence modifications as claimed are fully enabled, i.e., whether one of ordinary skill at the time of the present invention could have identified and made such substitutions and use recombinant antibodies that bind to a metal chelate (DOTA) on a common CDR (SEQ. ID. NOS.: 1 and 5) without undue experimentation. As discussed in detail above, the answer to this inquiry as applied to claims 1 and 37 is clearly yes, given the high level of skill and knowledge in the art at the time of the present invention, combined with the teachings of Applicants' specification.

Rejection under 35 U.S.C. 103(a)

Claims 1, 6, 8, 10-15, 24, 26-27, 30, 33-36 and 38-39 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Hansen et al. (WO 99/66951) in view of Chmura et al. (PNAS 2001; **98**: 8480-8484).

Applicants respectfully submit that it is improper to combine the teaching of Hansen et al. with those of Chmura et al. in order to establish a *prima facie* case of obviousness for the claimed invention, and, therefore, request the withdrawal of this rejection for the reasons set forth hereinbelow.

To construct a *prima facie* case of obviousness, the cited references must meet three criteria. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference must teach or suggest all of the claim limitations. *In re Vaeck*, 947 F.2d 488, (Fed. Cir. 1991). As stated in the May 3, 2007 memorandum from Margaret A. Focarino to the USPTO Technology Center directors, these elements must still be considered, even under the Supreme Court ruling for KSR Int'l Co. v. Teleflex, Inc., (No. 04-1350 (U.S. Apr. 30, 2007)), and that "in formulating a rejection under 35 U.S.C. §103(a) based upon a combination of prior art elements, it remains necessary to identify the reason why a person of ordinary skill in the art would have combined the prior art elements in the manner claimed." Applicants respectfully submit that each of the required criteria set forth above have not been satisfied and thus, a *prima facie* case of obviousness has not been set forth.

A. The Invention

As currently claimed, in several embodiments the invention provides an antibody that has an antigen recognition domain that recognizes a macrocyclic metal chelate. The antibody also includes a reactive site not present in the wildtype, within the antigen recognition domain. The metal chelate includes a reactive functional group. The reactive functional group is of a reactivity complementary to the antibody reactive site. The complementary reactive functional groups on the antibody and the chelate allow for the formation of a covalent bond between the antibody and the chelate upon recognition and binding of the chelate by the antigen recognition site of the antibody.

B. The combination of Hansen et al. and Chmura et al does not provide all elements of the claimed invention

The Examiner characterizes Hansen et al. as teaching a "bi-specific antibody which recognizes... a metal chelate such as DOTA." See Office Action, page 7, line 16. The Examiner also states that the present invention appears to recognize the same macrocyclic metal chelate as the prior art. See Office Action, page 7, lines 25-26.

Applicants respectfully disagree with the Examiner's characterization of Hansen et al. Hansen et al. teaches a bi-specific antibody, with one arm binding to a peptide carrier, in which the peptide carrier is the hapten. The peptide is attached to a metal chelate or chelating agent. The antibody is actually ***raised against***, and recognizes, the ***peptide carrier portion*** of the targetable conjugate (in several examples the *peptide*), not the chelate:

> "More usually, the antigenic peptide will have four or more residues, such as the peptide Ac-Phe-Lys(DTPA)-Tyr-Lys(DTPA)-NH_2. Again, the non-metal-containing peptide is used as an immunogen, ***with resultant Abs screened for reactivity against the Phe-Lys-Tyr-Lys backbone***." See Hansen et al., page 12, lines 3-6 (emphasis added).
>
> "In addition to hydrophilicity, chelates are chosen for their metal-binding properties, and are changed at will since, at least for those targetable conjugates whose bsAB epitope is part of the peptide or is a non-chelated hapten, ***recognition of the metal-chelate complex is no longer an issue***." See Hansen et al., page 23, lines 4-8 (emphasis added).

Thus, Hansen teaches antibodies which recognize peptides, and some of those peptides are disclosed as being bound to a metal chelate; however, Applicants submit that Hansen et al. does not teach an antibody either recognizing or irreversibly binding a DOTA chelate.

Because of the missing element of an antibody directly bound to a DOTA chelate, a *prima facie* finding of obviousness cannot be sustained.

C. Combining Chmura et al. with Hansen et al. to rectify the deficiencies of Hansen et al. is improper

The Examiner relies upon Chmura et al. to rectify the deficiencies of Hansen et al. Applicants respectfully submit that it is improper to combine Hansen et al. with Chmura et al. to rectify these deficiencies. Chmura et al. does not provide all of the limitations of the claims which Hansen et al. does not teach.

The Examiner states, "Hansen et al. does not explicitly teach that the antibody comprises a reactive site within the structure of the antibody that is not present in the wildtype of said antibody, wherein said reactive site is in a position within said antigen recognition domain. Nor does Hansen et al. teach that the macrocyclic DOTA contains a functional group which is reactive with the reactive site of

the antibody." See office action, p. 8, lines 3-7. The Examiner attempts to rectify these deficiencies with Chmura et al.

Chmura et al. cannot be relied upon to rectify these deficiencies. As the Examiner states, Hansen et al. does not teach that the macrocyclic DOTA contain a functional group which is reactive with the reactive site of the antibody. The Examiner is relying upon Chmura to rectify this deficiency, equating DOTA with the chelating agent of Chmura et al., EDTA. The Examiner is also equating the process for covalently attaching DOTA to an antibody with the process for covalently attaching EDTA to an antibody. Applicant submits that upon closer inspection these comparisons do not hold.

The Examiner has not made of record any art indicating that EDTA and DOTA are viewed as equivalent or obvious variations of each other. Under *In re Henze*, 181 F. 2d 196, 200-01 (CCPA 1950) and *In re Haas*, 580 F. 2d 461, there is a rebuttable presumption that adjacent homologs are obvious over one another. With respect to the compounds EDTA and DOTA, under *In re Haas* and *In re Henze*, these would not be deemed adjacent homologs obvious over one another: The structure of benzyl-EDTA is different from the chelate of the present invention. Cf. Chmura, Fig. 3 and claim 6. Benzyl-EDTA is an open chain, while the structure of the invention is a closed ring. In addition, there is no mention in Chmura et al. that the linkers which covalently attach EDTA to the antibody would also function to covalently attach DOTA to an antibody.

Given the specifity of the antibodies for their respective metal chelates (discussed further below) and the high level of those of skill in the art (as discussed above) EDTA and DOTA cannot be deemed as equivalents, nor can the process for covalently attaching DOTA to an antibody be equated with the process for covalently attaching EDTA to an antibody.

As the Examiner states, Hansen et al. does not explicitly teach that the antibody comprises a reactive site within the structure of the antibody that is not present in the wildtype of said antibody, wherein said reactive site is in a position within said antigen recognition domain. The Examiner attempts to rectify this deficiency with Chmura et al. The Examiner is equating the antibody containing reactive sites to covalently bind EDTA with the present invention. Again, Applicants submit that upon closer inspection this comparison does not hold.

The Examiner has not made of record any art indicating that the CHA255 antibody of Chmura et al. and the 2D12.5 antibody of the present invention are viewed as equivalent or obvious variations of each other. Chmura et al. teaches the covalent attachment of the chelate EDTA to an antibody with "high affinity" and "exquisite specificity" for(S)-benzyl-EDTA-indium chelates. *See*, Chmura, page 880,

second column, third paragraph. Because of the high specificity of antibody, it is highly unlikely that DOTA would be recognized by the antibody in Chmura et al. Again, EDTA is an open chained molecule, while DOTA is a closed ring. This is particularly of note as the present invention contains examples quantifying antibody affinity for different metal containing chelates. See specification example 3. Xray crystal structures of the CHA255-Indium-R1-benzyl-EDTA complex, and, separately, the 2D12.5-Yttrium-R2-benzyl-DOTA complex have been published. There is very little detailed similarity between them. The cysteine substitutions made by Chmura et al. on CHA255, and by Corneillie on 2D12.3 are on different chains and different CDRS. Corneillie et al, Bioconjug. Chem. 2004 Nov-Dec;**15(6)**:1392-402. Again, given the specifity of the antibodies for their respective metal chelates (discussed further below) and the high level of those of skill in the art (as discussed above) the CHA255 antibody and the 2D12.5 antibody of the present invention cannot be deemed as equivalents. Therefore, Chmura et al. cannot be relied upon to rectify the deficiencies of Hansen et al.

Assuming arguendo that the antibody of Hansen et al. recognized the metal chelate of Chmura et al., the metal chelate would not be able to covalently bind: the metal chelate reactive functional group in Chmura et al. would necessarily have been bound to the peptide (Hansen) instead of to the mutant reactive site of the antibody. If a proposal for modifying the prior art in an effort to attain the claimed invention causes the art to become inoperable or destroys its intended function, then the requisite motivation to make the modification would not have existed. *See In re Fritch*, 972 F.2d at 1265 n.12 ("A proposed modification [is] inappropriate for an obviousness inquiry when the modification render[s] the prior art reference inoperable for its intended purpose."). Accordingly, were Hansen et al. combined with Chmura et al., the reactive functional group of the chelate in Chmura et al. would no longer be available to react with the antibody and form a covalent bond. Therefore, Chmura et al. is not available to rectify the deficiencies of Hansen et al.

Read most broadly, the references teach forming a covalent bond between a bi-specific antibody and a peptide sequence bound to benzyl-EDTA, not the covalent attachment of DOTA metal chelates to an antibody with affinity for DOTA metal chelates.

D. No motivation to combine Hansen et al. with Chmura et al.

As the Examiner will appreciate, some motivation to select the claimed species or subgenus must be taught by the prior art. MPEP §2144.08(II)(A)(4)(a). Hansen et al. and Chmura et al. fail to provide the necessary motivation to incorporate Chmura's description of an antibody that forms a covalent bond with a metal chelate into the bi-specific antibodies of Hansen et al.

In the present invention, the chelate hapten is covalently bound to the antibody after the recognition of the hapten by the antibody. The peptide hapten of Hansen et al. does not covalently bind to the antibody. Moreover, Hansen et al. does not does not identify a problem which could be ameliorated by covalently binding the peptide hapten to the antibody. Nor does Hansen et al. speculate about techniques to increase the binding of antibodies to their targets. There is no suggestion in Hansen et al. that the described antibody can be covalently attached to a metal chelate or any other hapten. Similarly, there is no suggestion in Chmura et al. to use the disclosed antibody or metal chelate with a bi-specific antibody. Nor is there any suggestion in Chmura to incorporate a cyclic metal chelate such as DOTA into a covalent complex with a mutant antibody. Taking a single element from a first reference and combining it with the teachings of another reference if there is no suggestion in either reference to make such a combination is improper. Here, Hansen describes a bi-specific antibody raised against a peptide-chelate-conjugate (the metal chelate is not the peptide), and Chmura et al. describe benzyl-EDTA covalently attached to an antibody raised against benzyl-EDTA. Thus, there is no motivation to combine Hansen et al. with Chmura et al.

In addition, as stated above, combining Hansen et al. with Chmura et al. would require removing required elements of the antibody in Hansen et al. (the peptide from the peptide-chelate-conjugate). In other words, in order to combine the teachings of these references, the conjugate of Hansen et al. would essentially need to be "disassembled" to accommodate the teachings of Chmura et al. and reach the claimed invention. As provided in MPEP §2143A:

> The rationale to support a conclusion that the claim would have been obvious is that all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods *with no change in their respective functions*, and the combination yielded nothing more than predictable results to one of ordinary skill in the art. (emphasis added).

Clearly, combining Hansen et al. with Chmura et al. would require a change in the function of Hansen et al. (removal of the chelate from the peptide-chelate-conjugate), thus there is no rationale to support a conclusion that Hansen et al. and Chmura et al. render the instantly claimed invention obvious. As a result a skilled artisan would not have been motivated by the possibility of generating an "antibody having infinite affinity for a ligand which is applicable to other ligand binding pairs." See office action, page 8, lines 25-30.

Further, combining Hansen et al. and Chmura et al. would not allow one of skill in the art to "at once envisage" the claimed invention. When a reference broadly discloses a compound but does not specifically name a claimed compound, one of ordinary skill in the art must be able to "at once envisage" the claimed compound before it will be deemed anticipated. *See In re Petering*, 301 F.2d 676 (CCPA 1962). Chmura et al. describes the covalent attachment of EDTA to an antibody, not the metal chelate DOTA. Hansen et al. broadly discloses chelates such as DTPA and DOTA, but does not describe an embodiment that includes DOTA covalently bound to an antibody. There is no suggestion in Hansen as to why one of skill in the art would choose DOTA to combine with the teachings of Chmura et al. Assuming there was some suggestion in Hansen et al. to search for another reference to combine with Hansen et al., one of skill in the art would not choose Chmura et al. to do so because of the differences in structure between EDTA and DOTA. In addition, combining Hansen et al. and Chmura et al. would not allow one of skill in the art to "at once envisage" the claimed compound, because in order to combine the teachings of these references, the peptide-chelate-conjugate would essentially need to be "disassembled" to accommodate the teachings of Chmura et al. and yield the claimed composition. As such, one of skill in the art would not be able to "at once envisage" the claimed invention upon combining the teachings of these two references, and thus a finding of obviousness is not appropriate under *In re Petering*.

Further, Hansen et al actually teaches away from directly binding a metal chelate to an antibody. "Again the non-metal containing peptide is used as an immunogen." See Hansen et al, page 12, lines 4-6. The resultant antibodies are then, ". . . screened for reactivity against he Phe-Lys-Tyr-Lys backbone," not a metal chelate.

The only motivation for one of skill in the art to turn to Chmura et al. to provide the missing elements in Hansen et al. is provided by the instant specification. As will be appreciated, this is an impermissible use of hindsight. Under *In re Rouffet*, the Examiner must "identify specifically...the reasons one of ordinary skill in the art would have been motivated to select the references and combine them," *In re Rouffet*, 47 USPQ2d 1453, 1459, (Fed. Cir. 1998). The Examiner states that one of skill would have been motivated to make the modification "because Chmura et al. teach a method of generating an antibody having infinite affinity for a ligand which is applicable to other ligand binding pairs, wherein the antibody forms a covalent bond with the ligand which prolongs the lifetime of the complex." Office Action, pages 8 and 9. As the Examiner appreciates, this analysis necessarily defines a genus of antibodies with unlimited borders. Applicants have selected a particular species from this genus and this species is neither disclosed in or rendered obvious by the reference now of record. Applicants respectfully submit that because combining Hansen et al with Chmura et al. would require removing

required elements of the peptide-chelate conjugate in Hansen et al., a skilled artisan would not have been motivated by the possibility of the prolonged lifetime described in Chmura. Any possibility of prolonged lifetime from the combination of Hansen et al. and Chmura et al. would necessarily be countermanded by the need to disassemble the peptide-chelate conjugate disclosed in Hansenet al. Furthermore, since the conjugate in Hansen et al. requires elements that are not found in the claimed composition, there would be no reason to expect the prolonged lifetime described in Chmura et al. could also occur with the conjugates described in Hansen et al.

E. No reasonable expectation of success in combining the two references

The Examiner states that ". . . one of ordinary skill in the art would have a reasonable expectation of success that by modifying the anti-chelate antibody and chelate, e.g., DOTA, used in the method taught by Hansen et al. in view of the teaching of Chmura et al., one would achieve a method of prolonging the lifetime of the complex at the target site in vivo." See office action, page 9, lines 1-4. However, as stated above, Hansen et al. does not teach an antibody recognizing a metal chelate. Accordingly, one of skill the art would have no expectation of success in practicing the claimed invention by combining Hansen et al. and Chmura et al, because one of skill would not expect to be able to disassemble the peptide-chelate-conjugate complex of Hansen et al. to successfully use its disclosed antibody with the metal chelate of Chmura et al. As the Examiner will appreciate, "combining known prior art elements is not sufficient to render the claimed invention obvious if the results would not have been predictable to one of ordinary skill in the art." MPEP §2143A. Moreover, one of skill in the art would not expect an antibody specific for EDTA to bind DOTA.

Here, there is no motivation to select the antibody of Hansen et al. and then combine it with the metal chelate described in Chmura et al. ((S)-benzyl-EDTA-indium) because the antibody of Hansen et al. would not have recognized the metal chelate of Chmura et al.: the metal chelate of Chmura et al. is not similar enough in structure to the peptide-chelate-conjugate complexes described in Hansen et al to suggest one of skill in the art that such elements could successfully be combined. The only motivation to combine these elements from Hansen et al. and Chmura et al. is found by referring to the instant specification, which is an impermissible use of hindsight.

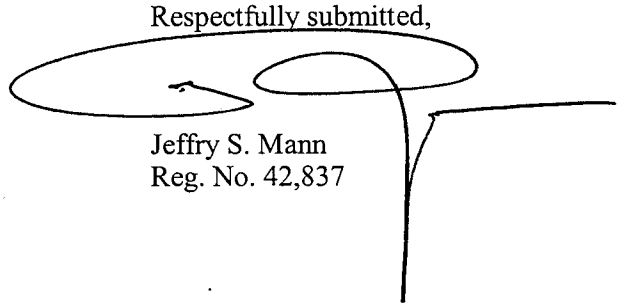
For at least the foregoing reasons, a finding of obviousness under §103(a) cannot be maintained, and Applicants respectfully request withdrawal of this rejection.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-442-1000.

Respectfully submitted,



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